

APPLICATION

of

ADRIAN SANDLER

for

LETTERS PATENT OF THE UNITED STATES

for

THERAPEUTIC PLACEBO ENHANCEMENT
OF COMMONLY-USED MEDICATIONS

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**THERAPEUTIC PLACEBO ENHANCEMENT
OF COMMONLY-USED MEDICATIONS**

CROSS-REFERENCE TO PROVISIONAL PATENT APPLICATION

[0001] The benefit of U.S. Provisional Patent Application Serial No. 60/249,973, filed November 20, 2000, is claimed.

BACKGROUND OF THE INVENTION

[0002] This invention relates to methods and kits for the treatment of medical disorders.

[0003] More particularly, it relates to methods and kits for the treatment of medical disorders utilizing reduced dosages of pharmaceutical without substantially reducing the effectiveness of the treatment.

[0004] Placebos (placebo means "I shall please") have always been integral to the healing practices and medicine. In an editorial of the British Medical Journal explicitly recognized the placebo as a legitimate and useful component of medical therapeutics. The rise of the placebo-controlled clinical trial since the 1960's focused attention on the benefits of specific therapies compared with placebo effects. Recent decades of medical research have demonstrated the ubiquitous effects of placebos. Powerful placebo effects have been demonstrated in a range of common medical conditions, including peptic ulcers,

irritable bowel, hypertension, low back pain, arthritis, anxiety disorders, depression and ADHD.

[0005] The mechanisms of placebo effects are poorly understood. It is known that there are no specific personality predictors of placebo response. Attributes of physicians, including their empathy and sense of confidence, can affect the magnitude of response. Responses to placebo in open trials are generally more robust than in controlled trials. Most importantly, the patient's expectation of improvement powerfully influences the response to placebo.

[0006] The results of a clinical trial involving children with Autism of secretin demonstrated no benefit of secretin over placebo. On several of the outcome measures, children in both the placebo and secretin groups showed significant improvement. Other studies of secretin have demonstrated robust placebo responses, including improvements in autistic behaviors and communication.

[0007] ADHD is a common condition in children, with estimated prevalence of 3% to 5%. Stimulants are widely used and very effective in the treatment of this condition. The most commonly prescribed stimulant is methylphenidate sold under the trade name Ritalin. Concerns about increasing sales of methylphenidate and potential side effects have generated public debate and controversy about overuse of stimulants.

[0008] Methylphenidate is effective in decreasing the symptoms of ADHD in 75% to 80% of children with this condition. Most children respond to a dose of 0.3 to 0.6 mg/kg/dose. At such low to moderate doses, about 10% to 30% of children experience one or more side effects, including loss of appetite, lack of weight gain, irritability, sleep disturbance, nausea or tics. These dose related side effects can be diminished or stopped by decreasing the doses of methylphenidate. Unfortunately, lower doses may be ineffective in treating the symptoms of ADHD.

[0009] There is extensive evidence from clinical trials of stimulants showing a robust placebo response in ADHD (Conners et al, 1996; Diamond et al, 1999). It is likely that the effect size is not a constant, but varies among individuals and also over time within individuals. A child who is a clinical responder to methylphenidate may be assumed to have a large component of his/her overall response due to specific effects of methylphenidate and a smaller component due to placebo. Thus it is desirable to take advantage of the "placebo effect" in the treatment of ADHD, as well as other disorders.

OBJECTS OF THE INVENTION

[0010] It is, therefore, one object of this invention to provide a method for reducing the normal dosage of a

pharmaceutical given to a patient for the treatment of a disorder without substantially reducing the effectiveness the treatment.

[0011] It is another object of this invention to take advantage of the placebo effect in reducing the normal dosage of a pharmaceutical without substantially reducing the effectiveness of the treatment.

[0012] It is still another object of this invention to provide a method which will take advantage of a patient's conditioned response and expectation of effectiveness in the treatment of a disorder, resulting in a reduction of the pharmaceutical needed for effective treatment.

[0013] It is further another object of this invention to provide a treatment of ADHD while reducing potential negative side effects of the treatment.

[0014] It is yet another object of this invention to provide a kit used in carrying out the methods stated in the above objects.

SUMMARY OF THE INVENTION

[0015] In accordance with one form of this invention, there is provided a method for reducing the normal dosage of a pharmaceutical given to a patient for the treatment of a disorder without substantially reducing its effectiveness. An initial dosage of the pharmaceutical is administered to the patient

during a first predetermined time period. A reduced dosage of the pharmaceutical is administered to the patient during a second predetermined time period. The reduced dosage has less pharmaceutical than the initial dosage. The second predetermined time period is subsequent to the first predetermined time period. A placebo is also administered during the second predetermined time period.

[0016] In accordance with another form of this invention, there is provided a kit for use in reducing the normal dosage of a pharmaceutical given to a patient for treating a disorder without substantially reducing the effectiveness of the treatment. A container is provided. At least a first unit having a reduced dosage of pharmaceutical is received in the container. At least a second unit having a placebo is also received in the container. Preferably, the kit includes a plurality of first units and a plurality of second units. Also, preferably, the second unit has distinctive indicia. Also, preferably, the kit contains written instructions coordinating the administration of the first and second units. It is also preferred that the patient is informed that the second unit containing the placebo may enhance the treatment of the disorder when taken with the first unit containing the reduced dosage of pharmaceutical.

[0017] In accordance with another form of this invention, there is provided a method for reducing the normal dosage of a pharmaceutical given to a patient for the treatment of the disorder without substantially reducing its effectiveness. A substantially normal dosage unit of pharmaceutical is administered during a first predetermined time period. A placebo unit is also administered during the first predetermined time period. A reduced dosage of pharmaceutical is administered during a second predetermined time period. A placebo unit is also administered during the second predetermined time period. The second predetermined time period is subsequent to the first predetermined time period.

[0018] It is preferred that a reduced dosage unit is also administered during a third predetermined period which is subsequent to the second predetermined time period. The reduced dosage unit administered during a third predetermined time period has indicia which is substantially the same as the indicia on the placebo unit, so that the patient's conditioned response and expectation of placebo-enhanced effectiveness is maintained.

[0019] In accordance with another form of this invention, there is provided a method for reducing the full dosage of a pharmaceutical given to a patient for the treatment of a disorder without substantially reducing its effectiveness by administering a placebo in association with a substantially decreased dosage of

the pharmaceutical to enhance the effectiveness of the pharmaceutical, thereby maintaining the effectiveness of the treatment as if the pharmaceutical had been administered at the full dosage level.

[0020] In accordance with another form of this invention, there is provided a method for reducing the full dosage of a pharmaceutical given to a patient for the treatment of a disorder without substantially reducing its effectiveness by administering a placebo in a unit bearing distinctive indicia, along with a unit having a full dosage of pharmaceutical, and then administering a placebo in a unit bearing distinctive indicia, along with a unit having a reduced dosage of pharmaceutical, whereby the visible distinctive indicia heightens the patient's conditioned response and expectation of effectiveness.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] The subject matter which is regarded as the invention is set forth in the appended claims. The invention itself, however, together with further objects and advantages thereof may be better understood in reference to the accompanying drawings in which:

[0022] FIGURE 1 is a block diagram illustrating one embodiment of the method of the subject invention;

[0023] FIGURE 2 is a plan view of a pill containing placebo having an enhanced indicia marked thereon;

[0024] FIGURE 3 is a plan view of a pill containing pharmaceutical having an enhanced indicia thereon;

[0025] FIGURE 4 is a top plan view of a kit illustrating one embodiment of the invention;

[0026] FIGURE 5 is a perspective view of the kit of Figure 4, however with the pills having been removed and omitting the dosage amount and day legends;

[0027] FIGURE 6 is a top plan view of a kit illustrating another embodiment of the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0028] In accordance with the preferred embodiments of the invention, there is provided a method and associated kit for reducing the normal dosage of a pharmaceutical given to a patient for the treatment of a disorder without substantially reducing the effectiveness of the treatment. While the specific research activity with respect to this invention, as discussed below, has been directed to ADHD, it is believed that this invention is applicable to many other disorders. For example, it is believed that the invention is applicable to other common medical conditions, including, but not limited to, peptic ulcers,

irritable bowel, hypertension, low back pain, arthritis, anxiety disorders and depression.

[0029] In addition, while the only two pharmaceuticals used in connection with the specific research activities with respect to ADHD were methylphenidate and dextroamphetamine, it is believed other pharmaceuticals, specifically central nervous system stimulants, may be used. Of course, other pharmaceuticals would be used in connection with the treatment of disorders other than ADHD, such as those disorders listed above.

[0030] Referring now more particularly to Figure 1, a block diagram is shown illustrating a preferred method of the invention. As shown in block 10, a full dosage of the pharmaceutical which, in the case of the treatment of ADHD, may be methylphenidate or dextroamphetamine, is administered to the patient, together with a placebo marked with enhanced indicia, during a first predetermined time period. The enhanced indicia may be the diamond shaped marking 12 on placebo pill 14, as illustrated in Figure 2. By administering the placebo marked with enhanced indicia, together with the full dosage, it is believed that the patient will associate beneficial effects of the pharmaceutical with the visually distinctive placebo through the repeated pairing of the pharmaceutical and the placebo. Thus the patient will develop a conditioned response to the placebo that is similar to the response the patient has from taken the

pharmaceutical. The first predetermined time period may vary. For example, it may be one day or one week.

[0031] During a second predetermined time period, as illustrated in block 16, the patient is given a reduced dosage of the pharmaceutical, together with a placebo also marked with enhanced indicia. The second predetermined time period should last at least approximately one week.

[0032] After the second predetermined time period, one may continue the treatment described in block 16, or one may administer a reduced dosage of the pharmaceutical marked with the enhanced indicia, as illustrated in block 18. A reduced dosage pill is illustrated in Figure 3. Pharmaceutical pill 20 has the diamond shaped enhanced indicia 12 printed thereon, which is identical to the indicia printed on the placebo pill.

[0033] It is important to inform the patient before the beginning of the treatment that the pill containing the placebo marked with the enhanced indicia may provide effectiveness when used with the pill containing the reduced dosage pharmaceutical. Thus the visually distinctive placebo heightens both the conditioned response and expectancy effects of the patient.

[0034] The step illustrated in block 16 may include a gradual reduction of the dosage of the pharmaceutical over a time period, such as a one week period. For example, an ADHD patient who has been on 20 mg of methylphenidate per day might receive

17.5 mg on the second day, 15 mg on the third and fourth days, 12.5 mg on the fifth and sixth day, and 10 mg on the seventh day and thereafter. During that one week period, each dosage of the methylphenidate is accompanied with a placebo pill having the enhanced indicia marked thereon. After the fourteenth day, the patient might continue to be given the 10 mg of methylphenidate, together with the placebo pill, or the patient may be converted to a methylphenidate 10 mg pill having the enhanced indicia printed thereon without the need to administer the placebo pill. As illustrated in Figure 4, the nonstandard dosages during Days 2 and 6 of methylphenidate might be accomplished by breaking off appropriate portions of a 10 mg pill to affect the reduced dosages.

Clinical Study

[0035] Twenty-six children with ADHD who were considered to have had a good treatment response to stimulant medication (e.g., methylphenidate) and whose parents were concerned about possible long-term side effects of stimulant treatment for their child were recruited to participate in a study comparing the effects of 50% dose reduction with a placebo "dose enhancer" to the effects of 50% dose reduction alone. Standardized parent and teacher ratings of ADHD behavior, parent ratings of side effects, and clinician ratings of treatment response were taken during

each experimental phase. Children were rated as significantly improved during the dose enhancer plus dose reduction condition in terms of both clinician global ratings of improvement and parent ratings of ADHD behavior. Side effects tended to diminish during the dose reduction conditions with no difference between the dose reduction alone and the dose reduction plus dose enhancer conditions. 40% of the children experienced at least a 33% improvement in symptoms during the dose enhancer condition (despite a 50% dose reduction), and 75% of these dose enhancer responders were returned to dose enhancer treatment by their parents at the end of the study.

[0036] Subjects were randomly assigned to one of two orders of the experimental conditions set forth below:

[0037] (1) BASELINE on current dose of medication of methylphenidate (one week), then 50% DOSE condition in which they received half of their baseline dose (one week), then 50% + DOSE ENHANCER (visually distinctive placebo) condition in which they received half their baseline dose and a dose enhancer pill (one week).

[0038] (2) BASELINE on current dose of medication (one week), then 50% + DOSE ENHANCER condition in which they received half their baseline dose

and a dose enhancer pill (one week), then 50% DOSE condition in which they received half of their baseline dose (one week).

[0039] During the experimental conditions, the child, the parents, and the study Physician were fully aware of the treatment conditions ("open label treatment"), and the parents and child were informed that "the dose enhancer pill may allow you / your child to get the effects of a full dose of your medicine while you only receive half of your dose of medication." The teachers were not informed of the experimental conditions ("single blind treatment"), and thus their ratings were presumed to be "blind" with respect to the different dose manipulations.

[0040] Once per week during each phase of these experimental conditions: (a) *parents* completed the IOWA CONNERS ADHD rating scale, and a stimulant treatment side effects rating scale; (b) the child's primary school *teacher* completed the IOWA CONNERS ADHD rating scale, and (c) the child was evaluated by the study *Physician* on the CLINICAL GLOBAL IMPRESSIONS scale. These scales are all standardized instruments for measuring drug treatment effects for children with ADHD.

[0041] The resulting data were analyzed by examining each outcome measure (parent IOWA ratings, teacher IOWA ratings, clinician CGI ratings, and parent side effects ratings) separately. Two statistical comparisons (t-test) were made for

each measure: (a) a comparison of the 50% dose to the 50% dose + dose enhancer conditions (testing if the addition of the dose enhancer resulted in better treatment during the dose reduction than did dose reduction alone), and (b) a comparison of baseline to the 50% dose condition (testing if dose reduction was associated with a worsening of symptoms).

[0042] (1) Parent Behavior ratings (IOWA Conners scale) - There was a marginally significant difference ($p = .07$) between 50% dose and 50% + Dose Enhancer (means 16.5 and 12.2, respectively) (lower number = less severe symptoms), and there was a marginally significant difference ($p = .08$) between Baseline and 50% dose (12.8 and 16.5, respectively). *This indicates that ADHD behavior tended to become worse when the dose of stimulant medication was reduced without a dose enhancer (baseline to 50% dose), but that ADHD behavior tended to remain the same when the dose of stimulant medication was reduced with the dose enhancer. This suggests that the dose enhancer can provide adequate symptom control during a period of dose reduction.*

[0043] (2) Teacher Behavior ratings (IOWA Conners Scale) - There were no significant differences between conditions; means - Baseline = 9.5, 50% dose = 8.9, 50% + Dose Enhancer = 10.0 (lower number = less severe symptoms). *This indicates that when not informed of changes in their student's*

dose of stimulant medication, teachers do not observe a change in their student's ADHD behavior. It further indicates that the dose reduction + dose enhancer condition did not results in a worsening of ADHD symptoms as reported by teachers.

[0044] (3) Side Effects Rating Scale - There were no significant differences between conditions. Baseline (mean = 7.3) was higher than both 50% dose (5.6) and 50% + Dose Enhancer (5.05) (lower number means less severe symptoms). This indicates that children were exhibiting some stimulant-related side effects while on their regular dose, and that the severity of these symptoms decreased when the dose was reduced by half.

[0045] (4) Clinical Global Impressions Scale - There was a significant difference ($p = .004$) between the 50% dose and the 50% + Dose Enhancer conditions (means 12.9 and 11.0, respectively) (lower number = larger improvement in symptoms + less side effects relative to baseline). This indicates that when considering the combination of treatment positive effects and drug-related side effects, children tended to do better overall during the dose enhancer condition.

[0046] (5) Individual subject analysis - A "responder" to the Dose Enhancer was defined as at least 33% reduction in parent behavior ratings coupled with no worsening in either teacher ratings or side effects during the dose enhancer phase. Eight subjects (40% of final sample) met criteria for responder.

Of these responders, all had a trend of reduced side effects during the dose enhancer phase with four / eight reporting large reductions in side effects. Of these responders, six had essentially no change in teacher reported behavior ratings, and two showed a reduction in teacher reported behavior ratings. Responder / Nonresponder status did not correlate with age, gender, stimulant type, baseline dose, or baseline side effects rating.

[0047] Approximately half of the children who underwent dose reduction with a dose enhancer demonstrated no noticeable deterioration as rated by teachers AND were also reported as BETTER by their parents in terms of both behavior and side effects.

The Kit

[0048] Referring now more particularly to Figures 4 and 5, there is provided kit 22 for providing the dose reduction treatment discussed above. The kit 22 includes an elongated container 24. A plurality of sub-compartments arranged in rows are provided for receiving pharmaceutical pills and placebo pills. Each sub-compartment, such as sub-compartment 24, is subdivided by a diagonal divider 28 and the pharmaceutical pill(s) 30 are placed on one side of subdivider 28 and the

placebo pill 32 is placed on the other side of subdivider 28, all within the same sub-compartment 26.

[0049] The kits illustrated in Figures 4, 5 and 6 contain two columns and seven rows of sub-compartments. Each sub-compartment is a row which represents a day. However, other combinations of rows and columns of sub-compartments can be utilized. For example, the kit may comprise sub-compartments in a seven by four matrix to accommodate different dosage or reduction treatments. As illustrated in Figures 4 and 6, each sub-compartment may have a particular day printed or embossed thereon. In addition, each sub-compartment may have the strength of the pharmaceutical printed or embossed thereon for each individual day.

[0050] In the example of the kit 22 shown in Figure 4, the patient is on methylphenidate 20 mg for the first day. Over the course of one week, the dosage is gradually decreased to 10 mg. The kit may be used for additional weeks to maintain the patient on this lower dose to ensure that the clinical effect is maintained. In kit 48 shown in Figure 6, which is substantially the same as the kit of Figure 4, except for the type of stimulant and the frequency of medication and placebo given per day, the patient is on dextroamphetamine 15 mg (oval) in the morning and 10 mg (round) in the afternoon for the first day. Using half tablets of these two doses (7.5 mg and 5 mg, respectively), the

doses are decreased over the course of one week to 50% of the original dose. The kit of Figure 6 could also be used to maintain these lower doses for an additional week, however, two additional columns of sub-compartments would be needed.

[0051] Each kit should include written instructions to coordinate the administration of the pharmaceutical containing pills and placebo containing pills. These instructions provide the dosage of stimulant therapy the patient should take during the dose reduction. For example, with the kit of Figure 4, the instructions state that on Day 1, the patient takes the usual doses of stimulant from sub-compartment 36. In this case, the stimulant is a 20 mg pill of methylphenidate, illustrated by pill 38. In addition, on the first day, the patient will take the so-called dose enhancer which is placebo pill 40, which is in sub-compartment 36, and as illustrated in Figure 4. The dosage of the stimulant will be reduced during the remainder of the week until it reaches 10 mg on Day 7. That is, the patient takes the 10 mg pill 42 which is within sub-compartment 44, as well as the placebo pill 46 bearing the enhanced indicia 12.

[0052] After the second week, as illustrated in row 34, where a patient takes a 10 mg pill of stimulant, as well as the placebo pill having enhanced indicia, the physician may have the patient take a 10 mg pill of stimulant with the enhanced

indicia 12 marked thereon, as illustrated in Figure 3 for the remainder of the therapy.

[0053] In addition, the patient should be informed by the written instructions and/or by the physician that the pill containing the placebo may enhance the treatment of the patient's disorder when taken with the pill containing the pharmaceutical.

[0054] Specifically in the treatment of ADHD, a physician prescribes a dose reduction kit, such as a kit shown in Figures 4-6, to help the patient onto a lower dose of stimulant therapy for ADHD. The patient is informed that this will involve the taking of a dose enhancer with each dose of stimulant that the patient takes. The physician may inform the patient that the dose enhancer is a small pill containing no active drug and is entirely harmless, and the patient should be informed that the pill containing the placebo may enhance the effectiveness of the stimulant drug.

[0055] Using this kit, the patient achieves a 50% reduction in stimulant while maintaining the desired effects of the stimulant in the treatment of ADHD.

[0056] From the foregoing description of the preferred embodiment of the invention, it will be apparent that many modifications may be made therein. It should be understood, however, that this embodiment of the invention is an exemplification of the invention only and that the invention is

not limited thereto. It is to be understood, therefore, that it is intended in the appended claims to cover all modifications as fall within the true spirit and scope of the invention.